REMARKS

Claims 1, 4, 7, 9, 10, 12, 13-16 and 18 are amended and claims 48-50 are added. The amendments are made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to pursue any canceled subject matter in a further application with the same rights of priority as the instant application.

Claim 1 is amended to recite a full-length chymosin pro-peptide and to clarify that the aspartic protease is capable of accurately cleaving the pro-peptide from the fusion protein. Claims 12 and 18 are revised to recite more clearly the embodiment where step c) is effected in vivo, in the milk, stomach or gut of an animal. Claims 48 and 49 are added to recite the embodiment where step c) is effected in vivo by expressing the aspartic protease in the host cell. Claim 50 is added to recite the embodiment where the aspartic protease of step c) is pepsin. The other claims are amended to make clerical changes that do not affect the scope of the claims.

The substantive amendments were discussed during the Examiner Interview held on July 28, 2005, and are believed to place the application in condition for allowance, as discussed in more detail below. Thus, their entry after final is respectfully requested. Upon entry of the amendments, claims 1, 4-10, 12-16, 18-19 and 48-50 will be pending. Applicant respectfully requests reconsideration of these claims in view of the following remarks.

Examiner Interview

Applicant thanks Examiner Steadman for the courtesies extended during the interview conducted on July 28, 2005. Applicant believes that the interview was quite helpful in advancing prosecution. Applicant's required statement of the substance of the interview is set forth below.

As reflected in the Interview Summary, Applicant proposed amending claim 1 to recite a full-length pro-peptide and/or to include an accuracy/specificity recitation with regard to

cleavage of the pro-peptide by the aspartic protease. As discussed during the interview, the prior art does not teach or suggest a method of preparing a recombinant polypeptide by producing a fusion protein comprising a full-length chymosin pro-peptide and the recombinant polypeptide, and contacting that fusion protein with a mature form of an autocatalytically maturing aspartic protease, itself capable of cleaving the pro-peptide accurately, whereby the pro-peptide is cleaved from the fusion protein to release the recombinant polypeptide.

Applicant also discussed the enablement of embodiments of the invention where step c) (contacting the fusion protein with the aspartic protease) is effected in vivo. Applicant explained how Example 3 evidences the enabling quality, as to those embodiments, of the original specification. In particular, Applicant noted that Example 3 shows cleavage of the pro-peptide from the fusion protein in the environment of a red turnip beetle gut extract, which, as Applicant emphasized, simulates in vivo conditions. Thus, those skilled in the art would understand from Example 3, with other teachings in the specification, that step c) can be effected in vivo, such as in the milk, the stomach, or the gut of an animal, as recited in claims 12 and 18.

Applicant believes that the foregoing claim amendments and the discussion during the interview overcome the issues raised in the Office Action. To ensure a complete response, Applicant addresses those issues below.

Claim Objections

The Office Action objected to Claim 12 for not being presented in the required marked-up format. The new claim listing presents claim 12 in the required marked-up format. Applicant therefore believes that this objection is obviated.

Indefiniteness Rejection

The Office Action rejected the claims for alleged indefiniteness with respect to the definition of "pro-peptide" as including functional portions of a pro-peptide. Applicant disagrees with the assertion that a functional portion of a pro-peptide (as defined in the

specification) could consist of a single amino acid residue. Nevertheless, to expedite prosecution, Applicant has amended claim 1 to recite a full-length chymosin pro-peptide. Applicant therefore believes that this rejection is obviated.

Enablement Rejection

The Office Action rejected claims 10, 12, 16 and 18 for alleged lack of enablement with respect to embodiments of the invention where step c) is effected in vivo. Applicant respectfully traverses this rejection.

Claims 10 and 16 recite that step c) (contacting the fusion protein with a mature form of an autocatalytically maturing aspartic protease) is conducted in vivo. The Office Action acknowledges enablement of embodiments where this step is effected by co-expressing the aspartic protease in the host cell (as recited in new claims 48 and 49), but alleges that the specification does not enable "any" means for effecting this step in vivo.

The primary basis of this rejection appears to be the alleged lack of working examples illustrating methods of effecting step c) in vivo. However, working examples are not required to satisfy § 112. Moreover, as discussed during the Examiner Interview, Example 3 supports in vivo embodiments by showing cleavage of the pro-peptide from the fusion protein in red turnip beetle gut extract. As noted above, although Example 3 was conducted in vitro, it simulates the in vivo conditions of the gut. Those skilled in the art will understand from Example 3 and other teachings in the specification that step c) can be effected in vivo, such as in the milk, stomach or gut of an animal (as recited in claims 12 and 18).

In view of the objective teachings in the specification regarding the ability to effect step c) in vivo, the illustration and guidance provided by Example 3, and the level of skill in the art, Applicant respectfully submits that claims 10, 12, 16 and 18 are fully enabled. Applicant therefore urges the Examiner to reconsider and withdraw this rejection.

§102 Rejection

Claims 1, 4, 6-9, 13, 15 and 19 were rejected under §102(b) as allegedly anticipated by Walsh. Applicant respectfully traverses this rejection.

As discussed during the interview, Walsh discloses the use of the chymosin-sensitive sequence of bovine k-casein as a cleavable linker for fusion proteins, but does not teach or suggest the use of a chymosin pro-peptide for such a purpose. Although the Office Action asserted that the Phe residue of the Phe-Met cleavage site of Walsh's fusion protein might constitute a "functional fragment" of a chymosin pro-peptide, Applicant explained during the interview that a functional fragment, as defined in the specification, could not constitute a single amino acid residue. (If that were the case, then cleavage would occur at every occurrence of that amino acid in the fusion protein, i.e., at each Phe residue.) Moreover, as noted above, instant claim 1 recites a full-length chymosin pro-peptide. Because Walsh does not teach or suggest a method of making a recombinant polypeptide that comprises producing a fusion protein comprising a full-length chymosin pro-peptide, the §102 rejection should be withdrawn.

§103 Rejections

Claims 1, 4, 6-9, 13, 15 and 19 were rejected under §103 as allegedly obvious in view of Ward and McCaman. Claim 5 was rejected as being obvious in view of Ward, McCaman and Fine or Walsh and Fine. Claim 14 was rejected over Walsh and Dunn or Ward, McCaman, and Dunn. Applicant respectfully traverses these rejections.

Claims 1, 4, 6-9, 13, 15 and 19 (Ward & McCaman)

The combination of Ward and McCaman does not teach or suggest the invention recited in claims 1, 4, 6-9, 13, 15 and 19, as shown below.

Ward is cited for teaching a nucleic acid encoding a fusion protein that includes a bovine chymosin prosequence as a cleavable linker. As recognized by the Examiner, Ward does not teach or suggest the use of mature chymosin or any other mature form

of an autocatalytically maturing aspartic protease to cleave the chymosin prosequence from the fusion protein. Indeed, Ward does not provide any specific teachings of how to cleave the bovine chymosin prosequence from its fusion protein. Instead, Ward states that "[t]he cleavable linker may then be cleaved using techniques known in the art." Ward, col. 14, lines 28-31.

The Office Action does not cite and Applicant is unaware of any prior-art reference that suggests the use of a mature form of an autocatalytically maturing aspartic protease, such as mature chymosin, to cleave a chymosin pro-peptide from a fusion protein, as presently recited. Accordingly, the obviousness rejection is improperly founded on hindsight and should be withdrawn.

Although this rejection also relies on McCaman, that reference does not teach or suggest the use of a mature aspartic protease to cleave a chymosin pro-peptide from a fusion protein. McCaman relates to the autocatalytic activity of aspartic proteases, and in no way teaches or suggests the use of mature aspartic proteases to cleave an aspartic protease pro-peptide sequence, such as a chymosin pro-peptide sequence, from a fusion protein, as presently claimed. It is only Applicant who recognized the usefulness of mature aspartic proteases in that context, as the present specification amply discloses.

Applicant has explained before that, prior to the present invention, those skilled in the art had no expectation that a mature aspartic protease would be capable of accurately cleaving a chymosin pro-peptide sequence from a fusion protein. There was uncertainty as to whether a mature aspartic protease would release an intact recombinant polypeptide (i.e., whether the recombinant polypeptide would be cleaved at other sites) and as to whether a mature aspartic protease would precisely cleave the pro-peptide from the fusion protein (i.e., whether cleavage would result in undesired overhangs). The accurate cleavage reported in the specification (see, e.g., Examples 1 and 2) was therefore surprising and unexpected, and satisfies a long-felt need in the art for a method of accurately cleaving fusion proteins to release a recombinant protein of

interest. To further emphasize this aspect of the invention, claim 1 is amended to recite that the aspartic protease "is capable of accurately cleaving the chymosin pro-peptide."

The general uncertainty surrounding the ability to accurately cleave a cleavable linker from a fusion protein is reflected in Ward itself. For example, column 14 notes that "[i]n some embodiments, after cleavage . . . the desired polypeptides contain unwanted amino acids" that can be removed using "aminopeptidases and carboxypeptidases of differing specificities." These teachings further demonstrate that Ward does not teach or suggest a method as claimed, i.e., a method using a mature form of an aspartic protease that is capable of accurately cleaving a chymosin pro-peptide from a fusion protein. Thus, the combination of Ward and McCaman does not teach or suggest the present invention.

Claim 5 (Ward, McCaman & Fine or Walsh & Fine)

Claim 5 recites specific embodiments of the invention where the recombinant polypeptide is hirudin or carp growth hormone. The combinations of Ward, McCaman and Fine or Walsh and Fine do not teach or suggest this invention.

The teachings of Ward and McCaman and of Walsh, and their failure to teach or suggest the invention of claim 1, are discussed above. Fine is cited for teaching the recombinant expression of carp growth hormone. Fine's teachings, however, do not remedy the inability of Ward and McCaman or Walsh to teach or suggest the claimed method. Thus, the rejections of claim 5 over Ward, McCaman and Fine and Walsh and Fine should be withdrawn.

Claim 14 (Walsh & Dunn or Ward, McCaman, & Dunn)

Claim 14 recites specific embodiments of the invention where the aspartic protease is heterologous to the chymosin pro-peptide. The combinations of Walsh and Dunn or Ward, McCaman and Dunn do not teach or suggest this invention.

The teachings of Walsh, Ward and McCaman, and their failure to teach or suggest the invention of claim 1, are discussed above. Dunn is cited for teaching that a number of aspartic proteases have the ability to proteolytically cleave a recognition site having Phe in the P1 position. However, the teachings of Dunn (and other references cited in the Office Action) relating to the ability of mature aspartic proteases to cleave specific peptides at specific sites in no way teaches or suggests the invention recited in claim 14, which recites a method wherein a mature aspartic protease other than chymosin is contacted with a fusion protein comprising a chymosin pro-peptide sequence and cleaves the chymosin pro-peptide from the fusion protein to release a recombinant polypeptide of interest.

As stated above, there simply is no hint in the prior art of using a mature aspartic protease to cleave a chymosin pro-peptide sequence from a fusion protein, releasing a recombinant polypeptide of interest. The fact that mature aspartic proteases have been shown to cleave specific peptides at specific sites in no way implicates the use of a mature aspartic protease in accordance with the present invention. As noted above, those skilled in the art had no reasonable basis for expecting that an aspartic protease would be capable of accurately cleaving a chymosin pro-peptide from a fusion protein, and did not know, for example, whether the aspartic protease would cleave the recombinant polypeptide at undesired sites and/or would cleave off too many or too few amino acid residues around the junction between the pro-peptide and the recombinant polypeptide. Without an assurance of accurate cleavage, there was no motivation to have employed an aspartic protease as presently claimed.

Because it is only the instant specification that recognizes and teaches that aspartic proteases are capable of accurately cleaving a chymosin pro-peptide from a fusion protein, this obviousness rejection is improperly founded on hindsight, and should be withdrawn.

Conclusion

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner like to discuss the matter, he is kindly requested to contact Courtenay Brinckerhoff at 202 295 4094 or Micheline Gravelle at 416 957 1682.

The Commissioner is hereby authorized to charge any deficiency in fees (including any claim fees) or credit any overpayment to Deposit Account No. 02-2095.

Respectfully submitted,

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